

REMARKS

Claims 1, 2, 5, 6, 9, 10, 13-17, 21-25, 30, 32, 34, and 37-49 constitute the pending claims, prior to Amendment. Claims 24, 37, 38, and 39 have been amended to more particularly point out that the anti-hedgehog antibodies for use in the claimed methods are anti-Sonic hedgehog antibodies. Claims 22, 23, and 25 have been cancelled. Applicants reserve the right to prosecute claims of similar or differing scope.

Applicants add new claims 50-55. Claim 50 corresponds to previously pending claim 17, but has been rewritten in independent form. Claim 51 corresponds to previously pending claim 25, but has been rewritten in independent form. Claims 52 and 54 are directed to a particular route of administration, and more particularly point out certain embodiments of Applicants' invention.

Applicants' amendments and newly added claims are fully supported by the specification. No new matter has been entered. Applicants request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the previous office action.

1. Applicants note with appreciation that any objections or rejections that were not expressly maintained in this Office Action have been withdrawn.
2. The disclosure is objected to because page 21 contains a blank. Applicants' amendment to the specification is believed to obviate the objection.
3. Claims 1, 2, 5, 6, 13-16, 21-24, 30, 37, 38-44, and 46-49 are rejected under 35 U.S.C. 112, first paragraph, for allegedly failing to comply with the enablement requirement. Claims 1, 2, 5, 6, 13-16, 21-24, 30, 37, 38-44, and 46-49 are further rejected under 35 U.S.C. 112, first paragraph, for allegedly failing to comply with the written description requirement. Applicants traverse these rejections and contend that the rejections are moot in view of the amended claims.

The basis of these rejections is two-fold. First, the Examiner objects to the claims to the extent that they are not limited to anti-Sonic hedgehog antibodies, humanized anti-Sonic hedgehog antibodies thereof, and fragments thereof (See, page 3 of the Office Action). This aspect of the rejection would apply to claims 24, 37-44, and 46-47. However, this aspect of the

rejection would not apply to claims 1, 2, 5, 6, 13-16, 21-23, 30, 46, and 48-49 because these claims are already directed to particular anti-Sonic hedgehog antibodies (e.g., 5E1, humanized antibodies thereof, and fragments thereof). Applicants traverse this aspect of the rejection and contend that the rejection is moot in view of the amended claims.

Applicants maintain that the specification is broadly enabling such that one of skill in the art would be able to readily make and test a range of antibodies and select antibodies for use in the claimed methods. Nevertheless, to expedite prosecution, Applicants have amended claims 24, 37, 38, 39 (and claims dependent thereon) to more particularly point out certain embodiments of the claimed invention. Specifically, Applicants have amended the claims to more particularly point out that the agents for use in the claimed methods are selected from anti-Sonic hedgehog antibodies, humanized anti-Sonic hedgehog antibodies, and fragments thereof. Applicants additionally note that new claims 50-55 are directed to the use of various anti-Sonic hedgehog antibodies. As such, new claims 50-55 are fully compliant with the enablement and written description requirement.

Applicants' amendments are not in acquiescence to the rejection. Applicants reserve the right to prosecute claims of similar or differing scope. Applicants' amendments are believed to obviate this aspect of the rejections under 35 U.S.C. 112, first paragraph. Reconsideration and withdrawal of these rejections are requested.

The second basis for the rejection is that the specification and the level of skill in the art allegedly fail to enable the claims throughout the scope of epithelial cells. This aspect of the rejection would apply to claims 1, 2, 5, 6, 13-16, 21, 30, 37, 38, 40-42, and 47-49. However, this aspect of the rejection would not apply to claims 9, 10, 17, 24, 32, 34, 39, 43-46, and 50-52 because these claims are already directed to particular epithelial cell types. Applicants additionally note that new claims 50-55 are directed to the use of various anti-Sonic hedgehog antibodies to modulate particular epithelial cells types. As such, new claims 50-55 are fully compliant with the enablement and written description requirement. Applicants traverse this aspect of the rejection.

The Wands factors are the appropriate criteria for assessing whether the level of experimentation needed to practice the claimed invention is undue. The Wands factors include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the subject matter at issue, (5)

the state of the prior art, (6) the relative skill of those in the art, and (7) the predictability or unpredictability of the art. Applicants submit that the claims are enabled throughout their scope in view of consideration of these factors.

The specification provides an extensive discussion of the various epithelial cell types that can be modulated using anti-hedgehog antibodies, as well as methods of making and testing anti-hedgehog antibodies to identify the antibodies for use in modulating the tissues presently claimed. The specification additionally provides working examples indicating that anti-hedgehog antibodies can be effectively used to modulate hair growth. As such, the specification provides extensive guidance to enable the skilled artisan to practice the claimed invention.

Applicants note that, as of the filing date of the instant application, the level of skill in the art was very high. In view of the high level of skill in the art of developmental biology and molecular biology, Applicants contend that one of skill in the art would readily be able to practice the claimed invention based on the specification.

The enablement requirement does not require that one of skill in the art can practice the claimed invention without any experimentation. The enablement requirement merely requires that one of skill in the art can practice the claimed invention without undue experimentation.

The quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether undue experimentation is required to make and use the invention. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.' *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

In view of the detailed disclosure in the specification, including the presence of working examples, and in view of the high level of skill in the art, Applicants contend that the level of experimentation required to practice the claimed invention throughout a range of various epithelial cell types does not constitute undue experimentation.

In further support of Applicants' contention that the practice of the claimed invention does not involve undue experimentation, Applicants enclose herewith abstracts from articles

detailing the role of Sonic hedgehog signaling in various epithelial cell types (Khan et al., 2007; Grachtchouk et al., 2006; Lees et al., 2005; and Stepan et al., 2005, enclosed herewith as Exhibits 1-4). Briefly, Khan et al. provide a study of Sonic hedgehog signaling in the molar tooth root (e.g., dental epithelium). Grachtchouk et al. provide a study of hedgehog signaling in odontogenic keratocysts of the jaw which are epithelial in origin. Lees et al. provide a study of hedgehog signaling during normal and pathological development and maintenance of the adult gastrointestinal tract. Stepan et al. provide an analysis of the regulation and function of Sonic hedgehog in gastric epithelial cell differentiation. These references are merely exemplary of the post filing evidence that shows that, as detailed in the specification, modulation of hedgehog signaling can be used to modulate growth and differentiation in a variety of epithelial tissues.

Applicants contend that the claims are enabled throughout their scope. In view of the guidance provided by the specification, the level of skill in the art, and the presence of working examples in the specification, Applicants contend that one of skill in the art could readily practice the claimed invention throughout the range of epithelial cell types presently claimed.

Applicants' amendments and arguments above are equally applicable to the written description rejection. In view of Applicants' arguments and amendments, reconsideration and withdrawal of the rejections under 35 U.S.C. 112, first paragraph, are requested.

4. Applicants note with appreciation that the Examiner has indicated that claims 9, 10, 32, and 45 are allowed.

Applicants additionally note that the Examiner has indicated that claims 17, 25, and 34 are objected to as being dependent from a rejected base claim, but that these claims would be allowable if rewritten in independent form. Applicants note that new claim 50 corresponds to previously pending claim 17 and that new claim 51 corresponds to previously pending claim 25.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Please charge any further fees due or credit any overpayments to **Deposit Account No. 18-1945, under order no. CIBT-P01-114.**

Date: May 24, 2007

Respectfully Submitted,



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